Remarks

Applicants have amended claims as shown supra. Applicants provide herewith Table 1, wherein the specific support for the amended claims is indicated. Table 1 is attached herewith as an Exhibit A.

Applicants also introduce a set of new claims 39-48. Support for the new claims is shown in Table 2. Table 2 is attached herewith as an Exhibit B.

Accordingly, Applicants respectfully submit that neither the claim amendments nor the new claims introduce new matter and request that both the amendments and the new claims be entered.

Claims 30-33, and 36-38 have been cancelled without prejudice.

Applicants now turn to the specific rejections.

The Examiner rejected claims 11, 24-26, and 30-38 as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement. Specifically, the Examiner alleged that the specification does not describe "**that each copy has an identical generic oligonucleotide that is attached to the array's x and y coordinates**." (Page 4, lines 14-17 of the 5/28/08 Office Action.)

Applicants respectfully disagree. At page 10, lines 10-15, the specification reads that the "method contemplates a **solid support with positions for oligonucleotides defined by x and y coordinates**. At **each position** … a **oligonucleotide is immobilized**. In one embodiment… the **same oligonucleotide** (i.e., an oligonucleotide with the **same generic nucleotide** sequence) is **immobilized in every position**." (Emphasis added)

Applicants have amended the claims to change the term "identical" to term "same." With this amendment, the specification provides *verbatim* support for this claim.

As described in the method of making these arrays, the oligonucleotides serve as an "anchor" to attach the multiple copies of the unique target nucleic acids to the solid surface. As explained in the specification the "invention contemplates solving both problems [inconvenience of synthesizing long oligonucleotides and limited space in the x/y plane of any solid surface] by utilizing circular nucleic acid in the production of the array" (page 10, lines 10-11), the

specification further provides that "region having a sequence complementary to at least a portion of said generic oligonucleotide permits hybridization of the circular template to the immobilized oligonucleotide" (page 10, lines 19-23).

The Examiner also alleged that the specification does not describe a nucleic acid wherein "**at least two copies of each of the unique sequence of interest separated by a generic nucleic acid sequence in the terminus of each of immobilized oligonucleotides"** recited in claim 30. (Sentence bridging pages 4 and 5.)

Applicants respectfully disagree. The specification explicitly reads "said immobilized **oligonucleotide is** thereafter **being extended** to **create a unique extended** nucleic acid strand at each position on the solid support, such extended strands comprising **two or more... copies of sequence of interest**" (page 11, lines 1-5).

Applicants have amended claims to recite to term "two or more" rather than "at least two" to provide *verbatim* support for the claims, although Applicants sincerely believe that the meaning of these terms is interchangeable.

Claims have also been amended to further clarify them.

In view of the above, Applicants respectfully submit that the claims fully comply with the 35 U.S.C. §112, first paragraph, written description requirement.

The Examiner rejected claims 11 and 23-38 as allegedly not complying with 35 U.S.C. §112, second paragraph, definiteness requirement.

Specifically, the Examiner alleged that in claims 11, 23 and 30, it is "unclear whether there is/are one or more of the immobilized oligonucleotides extending in the array' s x or y dimension or not." (Page 5, par. 11.)

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The claimed invention is directed to "an array" of nucleic acid sequences on a solid surface, where the surface coordinates are x and y. The term "array", to any one skilled in the art, means a selection of plurality of templates, in this case nucleic acids on the solid surface. As such, it is clear to any one with ordinary skill in the art that more than one nucleic acid must be

attached to the solid surface, wherein each nucleic acid is located on different position, i.e., has different x and y coordinates. The specification also provides that the "method contemplates a solid support with **positions [plural]** for **oligonucleotides [plural]** defined by **x and y coordinates [plural]**" (page 10, lines 10-11, emphasis added). The claims also refer to plurality of oligonucleotides.

Moreover, as acknowledged by the Examiner, the array is a three-dimensional structure (page 7, line 2, of Office Action dated 5/28/08). The specification clearly sets forth that each of the plurality of the nucleic acid sequences on the array is located in x/y location wherein the oligonucleotide with multiple copies of the target extends from the solid surface "up from the surface", i.e., to the z-dimension (see, e.g., page 10, lines 25-29, and page 11, lines 1-6). Thus the array comprises multiple nucleic acid sequences each of which is a concatamer comprising two or more copies of a target nucleic acid (see, e.g., page 16, lines 22-24).

In addition, to expedite prosecution, Applicants have amended claims to include the term "plurality" before the term "immobilized oligonucleotides." *Verbatim,* support for this amendment can be found, for example in the original claims 1-11, and on page 12, line 24.

Thus, Applicants respectfully submit that claims 11 and 23 fully comply with the definiteness requirements under 35 U.S.C. §112, second paragraph, and that the rejection should be withdrawn.

The Examiner also alleged that claims 11 and 23 are vague and indefinite in view of step (d), because it is allegedly unclear "**what is a growth strand in the claim**" (page 5, par 11).

Applicants have amended the claims to delete the reference to the "growing strand", which is superfluous in view of the reference to "z-dimension."

The Examiner also alleged that the following passage "does not make sense" (Par 12 bridging pages 5 and 6 of 5/28/08 Office Action):

> 'wherein each extended immobilized oligonucleotide has a position on the array defined by its x and y coordinates, and is extended in the z dimension, a growing strand, such that each extended immobilized oligonucleotide comprises at least

two copies of said unique sequence of interest extending in the z dimension by the circular DNA template having the unique sequence of interest'

To expedite prosecution, Applicants have amended claims as shown above to address alleged lack of clarity.

Moreover, the Examiner rejected claim 11 alleging that because the preamble of the claim requires that between each unique sequence of the interest there is at least one region that is complementary to at least a portion of the identical generic oligonucleotide and

"**does not require that the at least a portion of the identical generic oligonucleotide is attached to the array defined by x and y coordinates from z coordinate**, if at least one region that is fully complementary to at least a portion of the identical generic oligonucleotide attached to the array's x and y coordinates and the identical generic oligonucleotide is attached to the array by a chemical bond from x or y coordinate, multiple copies of a sequence interest extend along either x or y dimension and does not extend along z dimension which is opposite to the claim."

Applicants respectfully submit that the rejection be withdrawn for the following reasons.

As described in the specification (e.g., paragraph bridging pages 10 and 11), the array components for an embodiment claimed in claim 11 are as follows:

1. Solid surface wherein location of each nucleic acid sequence or "probe" can be defined using x and y coordinates; and
2. A plurality of nucleic acid sequences or a "probes" that are attached to the solid surface, wherein the "probe" has essentially three "parts":
   a. a nucleic acid sequence part that attaches the nucleic acid sequence to the solid surface (same for each of the nucleic acids sequences), this part also serves as a "primer" for the rolling circle;
   b. a nucleic acid sequence part that corresponds to a unique target sequence - this part is repeated two or more times in the immobilized "probe"; and

c. a nucleic acid sequence part that separates each copy of the unique target sequence and that is identical to at least part of the "primer" sequence - this sequence is introduced to the "probe" by the rolling circle method because the circular template used for the primer extension has to hybridize to the immobilized "primer."

Applicants have amended the claims to make these components more explicit. In view of the amendments to claim 11, Applicants respectfully submit that the rejection be withdrawn.

The Examiner further rejected claim 23. Specifically, the Examiner asked "why the different unique sequence of the sequence of interest in the sequence of interest can be complementary to itself" (page 7, last two lines of the 5/28 Office Action).

Applicants respectfully submit that the rejection be withdrawn for the following reasons.

As described in the specification, for example in paragraph bridging pages 11 and 12, the array components for an embodiment claimed in claim 23 are as follows:

1. Solid surface wherein location of each nucleic acid sequence or "probe" can be defined using x and y coordinates; and
2. A plurality of nucleic acid sequences or a "probes" that are attached to the solid surface, wherein the "probe" has essentially three "parts":

    a. a nucleic acid sequence part that attaches the "probe" to the solid surface (different for each probe), this part also serves as a "primer" for the rolling circle and therefore, in this embodiment, this "primer" must be complementary to the unique sequence that is present in the circular template used to make the array;

    b. a nucleic acid sequence part that corresponds to a unique target sequence - this part is repeated two or more times in the immobilized "probe"; and

    c. a nucleic acid sequence part that separates each copy of the unique target sequence and that is identical to at least part of the "primer" sequence - this sequence is introduced to the "probe" by the rolling circle method because the

circular template used for the primer extension has to hybridize to the immobilized "primer."

Applicants have amended claim 23 to clarify the components of the array and respectfully submit that the rejection be withdrawn.

In view of the amendments, Applicants respectfully submit that claims 11 and 23 now fully comply with 35 U.S.C. §112, second paragraph, definiteness requirement.

The Examiner rejected claim 30 alleging that "it is unclear that the terminus is the terminus of what."

Applicants respectfully submit that the rejection be withdrawn for the following reasons.

Applicants have amended claim 30 to delete the reference to the term "terminus" because it is redundant in view of the reference to z-dimension.

In view of the amendments, Applicants respectfully submit that claim 30 now fully complies with 35 U.S.C. §112, second paragraph, definiteness requirement.

The Examiner rejected claims 30-33 and 36-38 under 35 U.S.C. 102(e) as allegedly being anticipated by Smith *et al.*, (US Patent No. 5,753,439, filed on May 19, 2003)("Smith").

Applicants respectfully disagree. However, to expedite prosecution of preferred embodiments, Applicants have cancelled claims 30-33, and 36-38.

Applicants further submit that Smith does not apply to the new claims 39-56 for the following reasons.

Claim 39 is directed to an array of nucleic acid concatamers attached to a solid support. The nucleic acids attached to the surface are each different, but comprise a short "primer" nucleic acid sequence that is identical between each of the nucleic acid. This "primer" serves as an "attachment tool" to attach the unique nucleic acid sequence concatamers to the solid support. The different concatamer "probes" attached to the solid surface each carry a sequence of interest repeated two or more times. Between the sequence of interest repeat, there is a short nucleic acid region, a "separating region." This separating region is also identical in each of the "probes."

That is because the "separating region" has a sequence that is at least partially complementary to the "primer sequence" attaching the nucleic acid "probe" to the solid surface. However, because each of the sequence of interest or "target" that is repeated in the concatamer "probe" is different, each of the probes attached to the solid support is necessarily different.

In contrast, Smith teaches an array has the same trinucleotide repeat sequence repeated between two constant "primer" regions. The trinucleotide repeats are not separated by a "separating region."

The Examiner appeared to argue that in claim 30 this distinction is not claimed because "claim 30 does not require that the unique sequence of interest is different from the generic nucleic acid sequence" (page 11, lines 15-16 of the May 28, 2008 Office Action).

Applicants respectfully submit that this requirement is clear in claim 39. The fact that each of the "primer" attachment parts is identical between all the "probes" and each of the "separating sequences" are at least partially complementary to the "primer" sequence makes it impossible for the "primer" and the "target" to be identical. Therefore the unique sequence of interest is necessarily different from the generic nucleic acid sequence.

The difference is also evident from the significant difference in the function between the Smith array and the presently claimed array. Smith array is designed to detect the length of a trinucleotide repeat for diagnostic purposes, whereas the present arrays are directed to detect the number or amount of a certain target sequence in a nucleic acid sample.

In other words, in the array of Claim 39, each immobilized nucleic acid is unique and comprises a identical sequence segment attached to the array (Segment 1) followed by repeats of the sequence complementary to the unique target sequence (Segment 2) and the sequence segment that is at least partially complementary to the identical sequence segment (Segment 3). Hence, as shown in Figure 2, in one embodiment, the probe can be depicted as:

Segment 1-Segment 2- Segment 3-Segment 2- Segment 3-Segment 2- Segment 3…

In contrast, as illustrated in Figure 1, in the arrays of Smith, each probe can be depicted as: **Segment-A –Segment-B–Segment-B–Segment-B–…Segment-C**.

Claim 46 is directed to an array of unique immobilized nucleic acid sequences wherein **each** unique immobilized nucleic acid sequence comprises two main sequence segments,

namely, a sequence segment that is different for each immobilized nucleic acid sequence and attached to the solid support (Segment-1), and a sequence segment (Segment-2), following the attached sequence segment, that is complementary to a sequence of interest, is different for each immobilized nucleic acid sequence, and is more than 13 nucleotides long

The sequence segment that is complementary to a target sequence is repeated at least two times.

In contrast, the Smith arrays have an identical "primer" sequence (Segment-A) attaching the trinucleotide repeat "probes" onto the solid support, and the trinucleotide repeats (Segment-B) are followed by an identical 3' sequence (Segment-C), which is different from the 5' attaching sequence (Segment-A) and corresponds to a region that flanks the trinucleotide repeat in the target nucleic acid. A schematic description of an array of Smith is depicted in Figure 1.

Thus, in the arrays of Claim 46, each immobilized nucleic acid is unique and comprises a unique sequence segment attached to the array (Segment 1) and is followed by repeats of the sequence complementary to the target sequence (Segment 2). Hence, in one embodiment, the probe can be depicted as: **Segment 1-Segment 2-Segment 2- Segment 2..**. A schematic illustration of one embodiment of the arrays of Claim 46 is further illustrated in Figure 3. In contrast, in the arrays of Smith, shown in Figure 1, each probe can be depicted as: **Segment-A – Segment-B – Segment-B – Segment-B - Segment-C**.

Accordingly, Smith cannot anticipate claim 46.

Claim 50 is directed to an array of immobilized nucleic acid sequences wherein each of the "probes" are attached to the solid support by hybridization to a "primer" that has been attached to the solid surface. A schematic illustration of an embodiment of the arrays of Claim 50 is depicted in Figure 4.

As illustrated in Figure 1, Smith does not describe arrays, wherein the trinucleotide-repeat containing "probes" are attached to a solid surface by at least partially hybridizing the 5' flanking sequence to a complementary "primer" attached to the solid surface,.

Accordingly, Smith cannot anticipate claim 50.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is authorized to charge Nixon Peabody LLP Deposit Account No. 50-0850.

Respectfully submitted,

Date: November 26, 2008

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